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(54) Pre-filled injection device comprising a barrel wherein a liquid diazepam formulation is accomodated.

(57) The invention relates to a pre-filled injection device, comprising (i) a barrel which is open at each end in which, before using the device, a liquid diazepam formulation is accommodated in a sealed manner and which comprises at least one rubber sealing member to seal the said formulation, and (ii) an injection needle or a needle connection at the front end of the barrel, said sealing member being manufactured at least substantially from bromobutyl rubber.

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Pre-filled injection device comprising a barrel wherein a liquid diazepam formulation is accommodated.

The invention relates to a pre-filled injection device, comprising (i) a barrel which is open at each end and in which, before using the device, a liquid diazepam formulation is accommodated in a sealed manner and which comprises at least one rubber sealing member to seal the said formulation, and (ii) an injection needle or a needle connection means at the front end of the barrel.

As is well-known, diazepam has good pharmacotherapeutic properties and is hence generally used as a sedative, as a hypnotic and as a muscle relaxant. Useful formulations for the parenteral administration of diazepam have meanwhile also become available. These liquid formulations comprise, in addition to diazepam and water, auxiliary substances in the form of organic solvents and/or formulation agents. As a result of this a solution or emulsion of diazepam which is suitable for parenteral administration can be obtained by a correct choice and dosing of the auxiliary substances.

Such liquid diazepam formulations are often stored for considerable periods of time. As a result of this, suitable reservoirs are required in which the liquid can be accommodated in a sealed manner. Such reservoirs which usually are manufactured from glass or from a suitable synthetic material which is compatible with the diazepam formulation, are preferably sealingly closed by means of rubber sealing members.

Reservoirs which should permit the long-term storage of injection liquids are found in particular in pre-filled injection devices. There is an increasing demand for such injection devices which are supplied to the user while already filled with injection liquid. These so-called pre-filled injection devices should often be stored for long periods of time before being used and must hence be able to stand up against the conditions in which the devices are stored. This means that the injection devices should be able to still function properly after a storage term guaranteed by the supplier and that the contents of the injection devices, i.e., the injection liquid, may not have suffered any detrimental effects from the storage.

It will hence be obvious that high requirements have to be imposed on such injection devices for the prolonged storage of injection liquids, both as regards to the maintenance of mechanical properties of the injection device, and as regards the preservation of the injection liquid during the storage period. Much attention has been paid to the choice and optional pre-treatment of the rubber sealing members for the barrels of such injection devices in which the injection liquids are sealingly stored before use of the devices. Of course, the type of rubber must be completely inert with respect to the medicament to be injected, also during the often long storage period, but must moreover satisfy high requirements as regards the impermeability to gases, in particular oxygen, and be sufficiently resistant to the external influences to which the injection device is exposed during storage, for example, heat, air oxygen and light, in particular UV-light. In addition to the said physico-chemical requirements which the selected type of rubber must satisfy, the rubber sealing members should have certain mechano- dynamical properties. This applies in particular to the piston and to the stopper or stoppers optionally movable in the barrel, which on the one hand must well seal the injection liquid in the barrel before use of the injection device, but on the other hand must easily be movable in the barrel during use of the device. Of course, the shape of the piston and of the stopper(s) plays an important part in said easy movability in the barrel, as well as the desired pre-treatment, for example, with silicon oil. High demands should equally be made upon the mechanical properties of sealing members having a central diaphragm which bursts under pressure and then permits the injection liquid to reach the needle. It will be obvious that said diaphragm should remain its sealing function prior to use of the syringe, but should burst open at the proper instant to allow passage of the injection liquid.

Butyl rubbers including bromobutyl rubber and chlorobutyl rubber, can be used for the manufacture of pistons for injection devices; this is disclosed, e.g., in U.S. Patent Specification 4,381,779. Chlorobutyl rubber has been found to be an excellent material for the manufacture of sealing members for reservoirs, in particular for barrels for injection devices. Sealing members manufactured from chlorobutyl rubber satisfy the above-mentioned requirements excellently, while in general the medicaments present in the injection liquid do not experience any detrimental influence from prolonged contact with this type of rubber. Liquid diazepam formulations, i.e., diazepam formulations for parenteral administration, however, constitute an exception. As a matter of fact it has been found that the shelf-life of the said formulations, after prolonged contact with chlorobutyl rubber sealing members, leaves to be desired. This is a serious disadvantage because as a result of this not only the concentration of diazepam decreases during the storage period, as a result of which a smaller quantity of the therapeutic than is desired is injected, but also undesired by-products may be formed which may arrive in the patient's body.

It is the object of the present invention to provide a pre-filled injection device as defined in the opening paragraph, comprising a barrel, wherein a liquid diazepam formulation can be stored in prolonged contact with at least one rubber sealing member without unacceptable deterioration in quality of the said formulation taking place.

This object can be achieved by means of an injection device, comprising a barrel in which a liquid diazepam formulation, sealingly closed by at least one sealing member, is accomodated, which device is characterised according to the present invention in that said sealing member is manufactured at least substantially from bromobutyl rubber.

Bromobutyl rubber consists of a bromine-containing copolymer of isobutene and isopropene as a basic elastomer to which fillers, auxiliary substances, pigments and the like are added in certain concentrations to obtain the desired properties. After vulcanization a rubber quality is obtained which - like the chlorobutyl rubber described hereinbefore - has the properties required for sealing members, in particular sealing members for the barrels of injection devices. As will become apparent from the examples, however, bromobutyl rubber - in contrast with chlorobutyl rubber - causes no unacceptable deterioration in quality of a liquid diazepam formulation in prolonged contact herewith.

Many examples are to be found in literature of prefilled injectors in which the injection liquid is sealingly enclosed between a piston and a stopper with pierceable central portion said stopper being rigidly connected to the front end of the barrel. When using such an injector, said central portion is pierced so that the injection liquid can reach the injection needle and can be injected. In a favourable modified embodiment the stopper rigidly connected to the barrel comprises centrally a diaphragm which bursts under pressure and thus permits the injection liquid to reach the needle; an example hereof is to be found in Netherlands Patent Application No. 7603511 in the name of the Applicants. More recently, one has proceeded to enclosing the injection liquid between a piston and a stopper which is movable in the barrel; see, for example, Netherlands Patent Application No. 7714308, also in the name of Applicants. When such an injector is used, both the piston and the stopper and the intermediately situated injection liquid are removed forward in the barrel, in which the stopper is moved out of its sealing position and the injection liquid can reach the injection needle past the stopper. By using several stoppers, such injection device can be made suitable for accommodating therein several injection liquids which may not be in contact with each other during the storage period.

In such pre-filled injection devices, the liquid diazepam formulation can be stored in the barrel while enclosed between two rubber sealing members. According to the invention, these injection devices comprise two sealing members of bromobutyl rubber with which the diazepam formulation can be in prolonged contact without deterioration of the quality of said formulation.

Automatic injection devices - or autoinjectors -actually constitute a special category within the pre-filled injection devices. In fact, automatic injection devices are also pre-filled with injection liquid; they are, however, intended for being used by unqualified persons. For that purpose they are constructed so that the injection liquid can be administered automatically by a person not trained in giving injections. Consequently, automatic injection devices are designed first of all for use by persons who at a given instant, which is not known beforehand, have to administer an injection into their own body. These persons include, for example, soldiers after they have been exposed to an enemy warfare gas, for example, a nerve gas. However, many of the medicaments used in automatic injection devices show undesired side effects or are insufficiently or incompletely active in therapeutic dosages. For example, atropine or obidoxim is generally used in an attack with nerve gas in order to neutralise the toxic effects of organophosphate poisons, the active constituents of most nerve gases. However, these organophosphate poisons also cause paralyses or spasm conditions of the muscles which are insufficiently controlled by the above-mentioned medicaments. Therefore, the activity of the said medicaments is often made up with benzodiazepines, for example diazepam, which is known to have a muscle-relaxing activity. Diazepam in a liquid formulation, suitable for parenteral administration, is preferably accommodated in the injection device while separated from the other medicaments in view of the mutual compatibility. Suitable multi-compartment automatic injectors in which several injection liquids can be accommodated while separated from each other are disclosed, for example, in European Patent Applications 72057 and 219899, both in the name of the Applicants. In addition to the therapeutic activity mentioned herebefore, diazepam also has a sedative effect, as a result of which the fighting value of the soldiers at the front is restored. For this latter purpose the soldier in the field is preferably provided with a separate automatic injection device which is filled with a liquid diazepam formulation. Such an injector is especially intended for appeasing a buddy in the battle field who has panicked as a result of war acts or injuries: "buddy aid".

It will be obvious from the above that still considerably higher requirements regarding the reliability have to be imposed upon automatic injectors than upon pre-filled non-automatic injection devices. Such

injectors are usually stored for many years at a time and, moreover, will be kept by the potential users for long periods of time under varying conditions; not only the proper operation of the injection devices must be sufficiently ensured, but the contents of the autoinjectors, i.e., the injection liquid or injection liquids, must, of course, remain sufficiently intact to ensure the intended therapeutic activity.

The present invention therefore also relates more in particular to such an automatic injection device for the prolonged storage of a liquid diazepam formulation, comprising, in addition to a power source, a barrel which is open at each end, to the front end of which an injection needle is attached and in which a diazepam formulation is accommodated between rubber sealing members, the sealing members being manufactured at least substantially from bromobutyl rubber. It has been found that the stringent stability requirements mentioned hereinbefore can be satisfied when bromobutyl rubber sealing members are used in an automatic injection device.

As stated hereinbefore, bromobutyl rubber is a match for chlorobutyl rubber, known for this purpose, as regards the mechano-dynamic properties. This means that bromobutyl rubber is excellently suitable for the manufacture of piston and stoppers which, when using automatic injectors, must move in the barrel thereof so as to permit the injection liquids to be expelled. Automatic injectors, for example, as disclosed in the European Patent Applications 77057 and 219899 mentioned hereinbefore, in which the diazepam formulation is accommodated between two stoppers which are movable in the barrel or between a piston which is movable in the barrel and a stopper which is also movable herein, may hence advantageously comprise stoppers or a piston and a stopper which are manufactured from bromobutyl rubber.

The invention will now be described in greater detail with reference to the ensuing specific example.

EXAMPLE

Storage stability test of liquid diazepam formulations between rubber stoppers

A liquid diazepam formulation is prepared by making up 5 mg of diazepam, 0.4 ml of propylene glycol, 0.1 ml (100%) of ethanol, 0.015 ml of benzyl alcohol, 48 mg of sodium benzoate and 2 mg of benzoic acid with water to a volume of 1 ml. The pH of the resulting solution is 6.7. Rubber stoppers and a glass barrel which is open at each end and has a diameter of 11.4 mm are pre-treated in the conventional manner by washing, siliconising and sterilising. The barrel is then dispensed with the above diazepam formulation and sealed at each end by means of the rubber stoppers. For the experiments three types of rubber are compared with each other, namely chlorobutyl rubber (Cl-bu), and two qualities of bromobutyl rubber: Br-bu 1 and Br-bu 2. The barrels are stored at a given temperature for a given period of time, after which the diazepam concentration is determined by means of HPLC. The decrease of the diazepam content (in percent) is recorded in the Table A below. The analyses have been carried out in triplicate; the recorded data are average results.

TABLE A

Decrease diazepam content after ...(t) at ...(T)				
		% decrease diazepam using .. rubber		
T (°C)	t (weeks)	Cl-bu	Br-bu 1	Br-bu 2
31	13	5.9	2.7	2.9
41	6	6.7	2.7	2.9
41	13	11.4	3.3	3.7
61	3	19.1	5.1	5.3
61	6	25.3	6.5	7.0
61	13	42.2	12.1	14.9

The experiments have been repeated with a liquid diazepam formulation comprising 6 mg of diazepam instead of 5 mg diazepam. The results are recorded in Table B.

TABLE B

Decrease diazepam content after ...(t) at ...(T)				
		% decrease diazepam using .. rubber		
T (°C)	t (weeks)	Cl-bu	Br-bu 1	Br-bu 2
31	13	6.8	2.4	3.0
41	6	7.0	2.7	3.4
41	13	11.6	3.4	4.1
61	3	20.3	4.7	5.8
61	6	27.6	6.8	8.0
61	31	43.5	12.7	15.9

It will be obvious from the above results that the chlorobutyl stoppers cause a considerably larger decrease of the diazepam content than the stoppers manufactured from the two qualities of bromobutyl rubber. The diazepam concentration, namely 6 with respect to 5 mg/ml, has no essential influence on the said decrease.

Claims

1. A pre-filled injection device, comprising (i) a barrel which is open at each end in which, before using the device, a liquid diazepam formulation is accommodated in a sealed manner and which comprises at least one rubber sealing member to seal the said formulation, and (ii) an injection needle or a needle connection means at the front end of the barrel, said device being characterised in that said sealing member is manufactured at least substantially from bromobutyl rubber.

2. An injection device as claimed in Claim 1, in which the liquid diazepam formulation, before using the device, is sealingly accommodated between two rubber sealing members in the barrel, said device being characterised in that the sealing members are manufactured at least substantially from bromobutyl rubber.

3. An injection device as claimed in Claim 2 for the automatic injection of injection liquid under the influence of a power source, comprising, in addition to the power source, a barrel, which is open at each end, to the front end of which an injection needle is attached and in which a liquid diazepam formulation is accommodated between two rubber sealing members, said device being characterised in that the sealing members are manufactured at least substantially from bromobutyl rubber.

4. An automatic injection device, claimed in Claim 3, in which the diazepam formulation is accommodated between two stoppers which are movable in the barrel or between a piston which is movable in the barrel and a stopper which is also movable therein, said device being characterised in that both stoppers or the plunger and the stopper, respectively, are manufactured at least substantially from bromobutyl rubber.

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EUROPEAN SEARCH REPORT

Application Number

EP 90 20 0587

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X,D	US-A-4 381 779 (STERLING DRUG) * Column 3, lines 10-34; figures *	1,2	A 61 J 1/06 A 61 M 5/315
X	DE-A-3 103 897 (SCHREINER) * Claim 8; page 7, lines 12-23; figures *	1	
A,D	EP-A-0 072 057 (DUPHAR INT. RES.) * Whole document *	3	
A,D	EP-A-0 219 899 (DUPHAR INT. RES.) * Whole document *	4	
A,D	NL-A-7 603 511 (PHILIPS) * Whole document *	1	
A	GB-A-2 010 681 (PHILIPS) * Whole document * & NL-A-7 714 308 (Cat. D)	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 J
A 61 M

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	26-06-1990	BAERT F.G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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